REMARKS

Claims 1-7, 35-40, and 41-50 were pending. Claims 1, 35, 43, 49, 57, and 61 are amended herein, finding support in the original claims and in the specification at least at paragraphs **[0244]** to **[0246]**. Claims 2, 3, 38, 44, 45, and 50 are canceled herein. Applicants reserve the right to pursue amended and canceled material in subsequent prosecution.

New claims 62-69 are submitted herein. Support for new claims 62-67 can be found in the specification at least at Example 4. Support for new claim 68 may be found in the specification at least at paragraph **[0269]**. Support for new claim 69 may be found in the specification at least at paragraphs **[0042]**, **[0074]**, **[0075]**, **[0247]**, and **[0280]**. No new matter is entered herein.

I. Interview Summary

On November 16, 2006, there was a telephonic interview including the undersigned, attorney Tom Paul, and Examiners Chunduru and Benzion.

Issues discussed included clarification of the restriction. As addressed by the Board in the Decision mailed May 30, 2006 and in furtherance to the Action following the Decision, the Examiner continues to examine subsets of the claims using unequal scope despite the apparent restriction to SEQ ID NO:76. In the interview, Applicants again confirmed that each of the sequences are in fact considered by the Examiner to be separate inventions and therefore restricted. Applicants asserted that the sequences should be maintained in the same group and not separately elected out, but the Examiners maintained the finality of the restriction. Participants also discussed potential claim scope for a continuation in relation to the restriction issues in the present case.

No agreement was reached. Applicants thank the Examiners for the courtesy of the teleconference.

II. Status of the Application

Applicants acknowledge the Examiner's statements on page 2 of the Action that claims 1, 4-5, 35, 39, 40, 43, 46, 49, and 51-61 are linking claims that are examined with the elected species and elected SEQ ID NO:76. According to MPEP §809, linking claims are not

required to be canceled, and according to MPEP §821, all claims that the Examiner holds as not being directed to the elected subject matter are withdrawn from further consideration by the examiner in accordance with 37 CFR 1.142(b). Despite the restriction of the periaxin polynucleotide sequences to one single sequence, the Examiner fails to examine some of the claims in light of SEQ ID NO:76 ("The broad claims 1, 4-5, 35, 39, 40, 43, 46, 49, 51-61 are linking claims and have been examined. Examination of such claims was not limited to either the species or sequence election"; page 3 of the Action). To examine subsets of claims by different scopes following a restriction is improper practice.

To improve clarity of the issue, Applicants have amended the independent claims consistent with the restriction requirement to the periaxin polynucleotide comprising SEQ ID NO:76.

III. Decision by Board of Patent Appeals and Interferences

On May 30, 2006, the Board of Patent Appeals and Interferences issued a Decision on the appeal in the present case, Appeal No. 2006-0298. The Board vacated the pending rejections and remanded the application to the Examiner. Applicants acknowledge several issues raised by the Board. First, the Board directed the Examiner to "take appropriate action not inconsistent with the views expressed herein." Secondly, the Board recommended that the Examiner reconsider the rejections in view of the restriction requirement and election of species. In particular, the Board stated that if the restriction is not being withdrawn, analysis in the rejection should be "limited to that subject matter, i.e., the claims as they read on SEQ ID NO:76 and 247ΔC." The Board further asserts that in making the rejection the Examiner should establish a relationship between SEQ ID NO:76 and the other SEQ ID NOs and establish why an enablement for the other SEQ ID NOs does not apply to the elected SEQ ID NO:76. Finally, the Board asserts that the Examiner does not adequately address the methods of claims 35 and 49 that do not require diagnosis. Applicants are grateful to the Board for clarification of issues of prosecution of this case.

IV. Issues under 35 U.S.C. 112, first paragraph, Enablement

Claims 1-5, 7, 35-36, 38-40, 43-46, and 48-61 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully disagree and assert that the claims are enabled not only for the larger scope

employed by the Examiner for diagnosing myelinopathies using alterations in *any* periaxin polynucleotide but in the refined scope restricted by the Examiner of using a periaxin polynucleotide of SEQ ID NO:76 and a species mutation of 247ΔC. Applicants address each of the Examiner arguments as set forth in the Action and pursuant to the factors of *In re Wands* (858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

A. Nature of the Invention

The Examiner states the subject matter of the claims. The Examiner also characterizes claim 49 as not being a mere detection assay because the claim requires an association of a periaxin mutation with a myelinopathy. Applicants note that claim 49 has no element regarding a myelinopathy.

B. Amount of Direction and Guidance

The Examiner characterizes some aspects of the specification by noting at least the identification of several mutations in periaxin and their locations (such as, for example, at least FIGS. 4 and 9) and that based on commonly utilized methods in the art, mutations in periaxin sequences other than the exemplary ones provided may be identified (Page 6 of the Action). However, the Examiner alleges that despite such guidance the specification does not establish a statistically significant association between all of the specific mutations and any myelinopathy and also alleges that despite such guidance the specification does not establish a predictable correlation for association between any mutation in periaxin and any myelinopathy. However, Applicants assert that statistical significance is not a requirement for patentability and request that the Examiner provide evidence from any authority that states such is required. Concerning predictability, the predictable correlation is that the defect in a periaxin polynucleotide is associated with a myelinopathy, not just a defect in any gene. Applicants are not trying to claim periaxin for a wide range of diseases but those as part of a phenotypically narrow range of myelinopathies, which are closely related diseases.

Applicants provide considerable amount of direction and guidance in the specification to practice the invention. For example, in Example 1 (paragraphs **[0235]** to **[0241]**, Applicants provide materials and methods to practice exemplary embodiments of the invention, including obtaining the periaxin polynucleotide, mapping it, and screening for mutations, such as by PCR. Example 2 provides characterization of the *PRX* gene, including

a tissue expression profile, *in situ* hybridization by FISH, and sequencing. Example 3 provides teaching of *PRX* mutation analysis in 168 peripheral neuropathy patients who had tested negative for mutations in *PMP22, MPZ, GJB1, EGR2*, or *MTMR2*. Even though alterations in *PRX* are described for unaffected carrier family members, it is well-known in the field how to correlate a particular mutation with a disease.

Furthermore, Example 8 shows that *PRX* mutations are related to a spectrum of demyelinating neuropathies (in paragraph **[0268]**): "These two families confirm that putative loss-of-function mutations in *PRX* cause autosomal recessive neuropathies and ***broaden the spectrum of PRX-associated peripheral neuropathies***." (emphasis added) Also (in paragraph **[0273]**): "Similar to the spectrum of phenotypes observed with mutation of other genes associated with CMT and related inherited peripheral neuropathies, the clinical phenotypes manifested in patients with mutations in *PRX* include CMT myelinopathies and DSN." As such, Applicants note that the invention has been utilized to evaluate thousands of neuropathy patients during the last few years (Athena Diagnostics).

The Examiner further alleges that Applicants have not established that any periaxin mutation is associated with DSN and that there is no predictable correlation between any homozygous periaxin mutation and the disease or that two different mutations in compound heterozygotes are associated with myelinopathy in general. Applicants consider this an inaccurate statement, given that the specification teaches at least in paragraph **[0244]-[0247]** the corresponding mutations. Whether or not it is predictable is irrelevant, but one can predict based on the specification that at least compound heterozygotes will have defective periaxin and therefore will have myelinopathy. The Examiner acknowledges on page 6 of the Action that the specification provides evidence for compound heterozygotes and transitions associated with the specific types of myelinopathies being CMT and DSN (see the specification at least at page 65; Example 3), but CMT and DSN are merely exemplary myelinopathies, and, therefore, Applicants have provided more than sufficient guidance to associate homozygous or compound heterozygous mutations with myelinopathies.

Additional allegations by the Examiner include that the specification has not established that the presence of a single mutation in a single allele indicates susceptibility to or carrier of periaxin-associated myelinopathy. Again, the Examiner fails to appreciate that the specification shows that a carrier has a particular alteration (see, for example, paragraphs

[0244]-[0247]), but when a member of the family has two copies of that alterations or two different alterations, the individual is afflicted with myelinopathy. This situation is the definition of a carrier. The Examiner also continues to state that it is clear that mutations in periaxin exist that are not associated with myelinopathy. Applicants assert that the specification is clear that an individual must be homozygous recessive (have a mutation on each of the two alleles) for the individual to have myelinopathy. As such, claim 57 directs the method as identifying an alteration related to the individual as either having the myelinopathy or being a carrier. Also, claim 61 recites that the method identifies the individual as either having the myelinopathy or being a carrier dependent on there being an alteration in either both PRX alleles or in one allele, respectively. Many of the pending claims concern diagnostic embodiments that reflect that myelinopathy is diagnosed when an alteration is present in both PRX alleles. Such an embodiment utilizes classical genetics for autosomal recessive expression first elucidated by Gregor Mendel in the 1860's, and it is well-known and understood by the skilled artisan.

C. Presence of Working Examples

The Examiner acknowledges that the specification discloses a method of screening Prx mutations in family studies and acknowledged that they describe detected mutations, including a deletion and a transition in patients affected with peripheral neuropathy. Furthermore, the Examiner refers to a positive correlation between the presence of a periaxin polynucleotide with a mutation that results in a truncated periaxin polypeptide with myelinopathy, wherein the patients have two aberrant forms of periaxin polypeptides. The Examiner stresses, however, that no *specific* mutation is associated with any of the different types of myelinopathies "as exemplified by the example 8 in the specification" (see bridging sentence beginning on page 8 of the Action) and that the specification fails to show that all alterations are diagnostic or associated with myelinopathies or that all carriers having an alteration or mutation in periaxin would not be carriers of disease-causing mutations.

Concerning working examples, Applicants assert that even if one could argue that the specification did not provide enough of them, Applicants submit that examples may be either "working" or "prophetic", and compliance with the requirements for enablement under 35 U.S.C. 112 does not require that an example is disclosed, or that the invention be reduced to practice prior to filing, *Gould* v. *Quigg*, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed.

Cir. 1987) and M.P.E.P. 2164.02. Applicants, however, strongly assert that the present Examples do comply with 35 U.S.C. §112 and the invention was reduced to practice prior to filing of the priority document.

Applicants assert that a showing in the specification for all alterations to be diagnostic is not required, because Applicants have provided multiple exemplary mutations in periaxin (at least paragraphs **[0007]** and **[0008]**) ***and*** have provided multiple examples of periaxin polynucleotides with which to identify the mutations (at least paragraph **[0064]**) ***and*** have provided exemplary means of correlating alterations with the disease (at least paragraphs **[0244]**-**[0248]** and **[0264]** to **[0282]**). Therefore, plenty of working examples have been provided in the specification that were sufficient to inform the skilled artisan how to make and use the invention.

D. Level of Predictability in the Art

The Examiner refers to other genes in the art that when mutated are known to be associated with myelinopathy, but the Examiner contends that the art does not establish a predictable association that any specific periaxin mutation or any other gene establishes a predictable association of any specific mutation in periaxin or any other genes with all of the number of diseases of myelinopathy. The Examiner further states that the specification does not establish a statistically significant association with any of the disclosed mutations in periaxin and any specific form of myelinopathy such that the skilled artisan might be able to predictabily correlate which mutations in periaxin would be associated with a specific form of myelinopathy.

Again, it is not required to provide stastistically significant data for enablement of a claim; this is simply not the standard required by the USPTO. The scope of the enablement must only bear a "reasonable correlation" to the scope of the claims. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Applicants assert that a reasonable correlation certainly does exist, given that *PRX* shown with DSN and the highly related myelinopathies are within the scope of reasonable correlation, particularly given their art-recognized phenotypic similarities. Furthermore, given that others subsequently identified periaxin mutations in myelinopathies of the spectrum other than DSN and commensurate with Applicants' teaching, there is most certainly a reasonable correlation. Thus, the Examiner is

inappropriately requiring statistically significant data for enablement of a claim. Applicants also reiterate that the present invention does not concern all myelinopathies, but only those related to periaxin defects.

E. Quantity of Experimentation Necessary

The Examiner surmises that lack of guidance in the specification and the unpredictability in the art would mean that a skilled artisan would require a large amount of experimentation to practice the claimed invention. The Examiner contends that a large study would be required to determine which specific alteration or mutation in periaxin was associated with myelinopathy, and the study would be mainly trial and error analysis. However, Applicants reiterate that undue experimentation is not required to determine which nucleotide alterations are associated with myelinopathy. The Examiner contends that a large amount of trial and error would be required to determine which mutations are associated with the disease. A considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cirl 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976). In fact, time-consuming experiments are acceptable if the type of experimentation is standard in the art. An extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance. *In re Colianni,* 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977).

Yet further, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Wands*, 858 F.2d 737, 8 USPQ2d 1404 (Fed. Cir. 1985). Techniques in molecular biology and molecular diagnostics are, and were at the time of filing of the application, well known and understood in the art. In fact, it is well recognized "that the skill in the art of molecular biology is quite high" *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986). Therefore, in contrast to the Examiner's assertions, the experimentation is, in fact, routine.

F. Summary of Enablement

Applicants assert that sufficient guidance was provided in the specification at the time of filing to direct the skilled artisan how to identify mutations in periaxin that are associated

with myelinopathies. In indisputable support of this, Applicants note that multiple papers since the filing of the application teach periaxin alterations that are associated with myelinopathies other than DSN. For example, Guilbot *et al.* (2001) teach that periaxin is responsible for an autosomal recessive form of CMT disease; in fact, Guillot published approximately two months after the filing of Applicants' provisional application. Also, Kijima *et al.* (2004) determined that periaxin mutation causes early onset CMT. ***Given that Applicants taught in the original disclosure that alterations in periaixin are indicative of myelinopathies, these subsequent papers indicate that Applicants in fact did provide how to make and use the invention, and the claims are thus enabled.*** This is particularly valid given that, as noted above, independent claims 1, 35, 43, and 57 require that the myelinopathy results from or is associated with a periaxin alteration.

Thus, Applicants assert that the claims are in fact enabled and respectfully request removal of the rejection.

V. Issues under 35 U.S.C. 112, first paragraph, Written Description

Claims 1, 4-5, 35, 39, 40, 43, 46, 49, and 51-61 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the Applicants had possession of the invention at the time of filing. Applicants respectfully disagree.

In particular, the Examiner considers that the current claims encompass a genus of periaxin nucleic acids that comprise a large number of mutations that are not disclosed in the specification. Applicants remind the Examiner that the claims have been restricted to being in the sequence of SEQ ID NO:76 and, therefore, there are not so many nucleic acids as the Examiner alleges. The Examiner states that there is no common element or attributes of the sequences to permit selection of sequences as polymorphisms, but Applicants assert that the restricted SEQ ID NO:76 gives the skilled artisan plenty of structure to correlate a mutation therein with a myelinopathy. At the very least, the multiple examples of mutations provide the skilled artisan with insight as to regions of the periaxin polynucleotide that may effect a gene product resulting in myelinopathy.

The Examiner also states that in the application there is no description that would demonstrate conception of any nucleic acids "other than those expressly disclosed..." (Page

15 of the Action), yet Applicants' present claims encompass one of "those expressly disclosed"—the exemplary SEQ ID NO:76. Applicants also provide multiple examples of periaxin polynucleotides (paragraph **[0064]**) and mutations (paragraphs **[0007]** and **[0008]**) such that it was reasonably conveyed to the skilled artisan that Applicants had possession of the invention at the time of filing.

It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations. *In re Smythe*, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

VI. Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Applicant believes no fee is due with this response other than the fee for an Extension of Time of Three Months and the fee for the new claims However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P02086US1 from which the undersigned is authorized to draw.

Dated: Feb. 8, 2007

Respectfully submitted,

By _____

Melissa L. Sistrunk
Registration No.: 45,579
FULBRIGHT & JAWORSKI L.L.P.
1301 McKinney, Suite 5100
Houston, Texas 77010-3095
(713) 651-5151
(713) 651-5246 (Fax)
Agent for Applicant